

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

207103Orig1s000

CHEMISTRY REVIEW(S)

Ibrance (palbociclib) capsules,
75, 100, and 125 mg

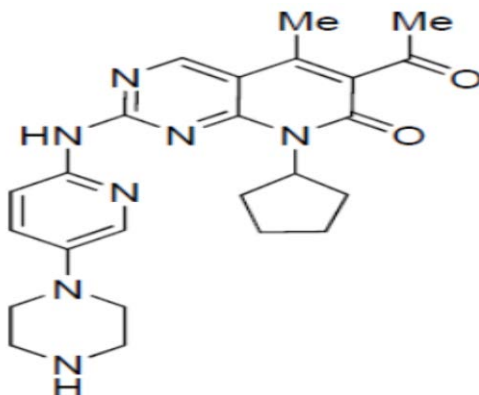
Summary Basis for Recommended Action
Chemistry, Manufacturing, and Controls
Date: January 20, 2015

Applicant: Pfizer, Incorporation
235 East 42nd Street,
New York, NY 10017

Introduction

Palbociclib is a new molecular entity indicated, in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

The chemical name for drug substance (palbociclib) is 2-Propenamide, N-hydroxy-3-[3-[(phenylamino)sulfonyl]-phenyl]-, (2E)-. Palbociclib has a molecular formula of C₂₄H₂₉N₇O₂ with a molecular weight of 447.54 Daltons. See structure below.



Ibrance (palbociclib) Capsules are available for oral administration in three strengths: 75 mg, 100 and 125 mg capsule. Ibrance (palbociclib) Capsules are supplied in 60 ml HDPE bottles of 21 capsules for all three strengths.

Drug Substance

Palbociclib is manufactured by a [REDACTED] (b) (4) [REDACTED]. Justification for the proposed starting materials is provided based on the discussion and the FDA comments at the EOP-2 meeting.

The Drug substance specifications were proposed as per ICH guidelines when applicable. Acceptance criteria are proposed primarily based on the manufacturing process capability, batch analysis data from the 27 batches produced using the proposed commercial process and considering the relevance to the clinical safety and efficacy. Stability studies for the drug substance demonstrated that palbociclib is physicochemically stable under both long term 25°C/60%RH (12 months) and accelerated 40°C/75%RH (6 months) conditions. No significant change or trending has been observed under either storage conditions. The proposed retest date of (b) (4) months stored (b) (4) is acceptable.

Drug Product

Ibrance (palbociclib) Capsules are available in 75 mg, 100 mg and 125 mg dosage strengths. The capsules contain palbociclib (a free base) as the active pharmaceutical ingredient together with microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin opaque capsule shells (with composition of gelatin, red iron oxide, yellow iron oxide, and titanium dioxide) and print ink. All three strengths of palbociclib capsules are formulated (b) (4)

(b) (4) in the three strengths, (b) (4)
Ibrance (palbociclib) Capsules are supplied in 60 ml HDPE bottles of 21 capsules for all three strengths.

Formulation development of Ibrance (palbociclib) Capsules was performed by Pfizer through two sites: Groton, CT, US and Freiburg, Germany. The basic steps in the manufacturing process consist of (b) (4)

(b) (4) Standard release specifications for a solid oral dosage form have been proposed. Pfizer Manufacturing Deutschland GmbH in Freiburg, Germany is the proposed commercial site for the drug product manufacturing, testing, packaging, and labeling.

The applicant submitted stability data from three primary registration batches for each of 75 mg strength, 100 mg strength, and 125 mg strength capsules up to 12 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the drug product in all three strengths packaged in HDPE bottles and stored at controlled room temperature. The submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

Related quality reviews:

- cGMP status of manufacturing facilities are acceptable
- Biopharm and Micro reviewers recommended approval

Conclusion: The NDA is recommended for approval from CMC perspective.

Ali Al-Hakim, Ph.D.
API Division Director (Acting),
ONDP, OPQ

NDA 207-103

**Ibrance (palbociclib) capsules,
75, 100, and 125 mg**

Pfizer, Inc.

CMC Review # 2

**Xiao H Chen, Ph.D (for Drug Substance)
Joyce Crich, Ph.D (for Drug Product)**

Review Chemists

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**Chemistry, Manufacturing, and Controls (CMC)
For the Division of Hematology Products**

Table of Contents

Chemistry Review Data Sheet.....	3
The Executive Summary	8
I. Recommendations	8
A. Recommendation and Conclusion on Approvability	8
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	8
II. Summary of Chemistry Assessments.....	8
A. Description of the Drug Product(s) and Drug Substance(s)	8
B. Description of How the Drug Product is Intended to be Used.....	10
C. Basis for Approvability or Not-Approval Recommendation.....	11
III. Administrative.....	11
A. Reviewer's Signature	11
Branch Chief's Signature	11
B. Endorsement Block.....	11
C. CC Block	11
Chemistry Assessment	12
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	12
S DRUG SUBSTANCE.....	12
P DRUG PRODUCT	12
A APPENDICES	12
R REGIONAL INFORMATION	12
II. Review of Common Technical Document-Quality (Ctd-Q) Module 1.....	12
A. Labeling & Package Insert.....	12
B. Environmental Assessment or Claim of Categorical Exclusion	16

Executive Summary Section

Chemistry Review Data Sheet

1. NDA 207-103

2. REVIEW #: 2

3. REVIEW DATE: 13-Jan-2015

4. REVIEWERS: Joyce Crich, Ph.D
Xiao H Chen, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents

Original IND 69,324 submission

CMC only Pre-NDA Meeting (23-Jan-2014) Minutes

Type B Pre-NDA Meeting (28-Feb-2014) Minutes

Document Date

10-Mar-2004

11-Feb-2014

31-Mar-2014

6. SUBMISSION(S) BEING REVIEWED:

Submission(s) Reviewed	eCTD Sequence Number	DARRTS SDN	Document Date
Rolling NDA Submission	0000	2	30-June-2014
Original NDA Submission	0003	5	13-Aug-2014
Amendment (response to FDA 12-Nov-2014 CMC IR)	0042	43	19-Nov-2014
Amendment (response to FDA 12-Nov-2014 CMC IR)	0048	49	26-Nov-2014
Amendment (response to FDA 02-Dec-2014 CMC IR)	0053	54	08-Dec-2014
Amendment (revised comparability protocol)	0059	61	23-Dec-2014
Amendment (revised comparability protocol)	0061	62	24-Dec-2014

Executive Summary Section

7. NAME & ADDRESS OF APPLICANT:

Name: Pfizer, Inc
Address: 235 East 42nd Street, New York, NY 10017
Representative: N/A
Telephone: (212) 733-2323

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Ibrance®
b) Non-Proprietary Name (USAN): palbociclib
c) Code Name/# (ONDC only): PXD101
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: small molecule inhibitor of CDK 4 and 6
for the treatment of advanced breast cancer

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 75 mg, 100 mg and 125 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

Executive Summary Section

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): palbociclib

Name (CAS): pyrido[2,3-*d*]pyrimidin-7(8*H*)-one, 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2-pyridinyl]amino]-

IUPAC Name: 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Other Name: *N*-hydroxy-3-(3-phenylsulphamoylphenyl) acrylamide

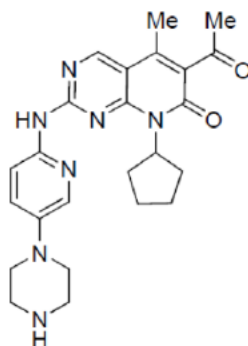
Company code: PXD101

(CAS) Registry Number: 414864-00-9, 866323-14-0

Mol. Formula: C₂₄H₂₉N₇O₂

Mol. Wt.: 447.54 g/mole

Structural Formula:



Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF # (b) (4)	Type	Holder	Item Referenced (b) (4)	Code ¹	Status ²	Date Review Completed	Comments
	IV			4	Adequate		See sections 1.4.1, 3.2.P.1 and 3.2.P.4
	IV			4	Adequate		See sections 1.4.1, 3.2.P.1 and 3.2.P.4
	III			4	Adequate		See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III			3 & 4	Adequate	20-May-2010 (by Dr. Y. Zhang)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III			3 & 4	Adequate	04-Feb-2014 (by Dr. Y-C Chen)	See sections 1.4.1 & 3.2.P.7
	III			3 & 4	Adequate	04-Feb-2014 (by Dr. X. Li)	See sections 1.4.1. & 3.2.P.7
	III			3 & 4	Adequate	25-Sep-2014 (by Dr. R. Frankewich)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III			3 & 4	Adequate	21-Mar-2012 (by Dr. G. Holbert)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Executive Summary Section

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	69324	Pfizer, Inc.	Palbociclib (PD-0332991)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-Nov-2014	Robert Wittorf
Pharmacology/ Toxicology	Degradation Products in Drug Product are acceptable*	See DARRTS for review*	Wei Chen
Biopharmaceutics	Acceptable	07-Jan-2015	Minerva Hughes
LNC	N/A		
Methods Validation**	Pending		
DMEPA***	The proposed proprietary name, Ibrance is acceptable	05-Sep-2014	Mathew Davis
EA	Categorical exclusion (see review)	29-Dec-2014	Joyce Crich
Microbiology	Approval from microbiology product quality standpoint	08-Dec-2014	Jessica Cole

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewer in her 30-Sep-2014 e-mail that the acceptance criterion for the degradation product (b) (4) in the drug product is qualified. See Section 3.2.P.5.6 for detailed information.

*Methods validation consult was sent to the FDA St. Louis Laboratory on 17-Sep-2014. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

***DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The Chemistry Review for NDA 207-103

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is recommended for approval. There are no outstanding CMC issues that impact approvability of this NDA.

Include the following language in the approval letter:

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (75 mg, 100 mg, and 125 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The chemical name for palbociclib is 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]-phenyl]-, (2*E*)-. Palbociclib has a molecular formula of C₂₄H₂₉N₇O₂ and a molecular weight of 447.54 Da. Palbociclib is a yellow to orange powder with pK_a of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly. Palbociclib is (b) (4) and requires (b) (4).

The (b) (4) of palbociclib was selected for development. Two other forms were identified during development ((b) (4)). No (b) (4) was found. (U) (4)

Palbociclib is manufactured by a (b) (4). Justification for the proposed starting materials is provided based on the discussion and the FDA comments at the EOP-2 meeting. Throughout the development the synthetic route (b) (4)

The proposed commercial process

Executive Summary Section

(b) (4) has been used to manufacture up to 27 batches for clinical supply including the pivotal clinical studies. Impurities formation during manufacturing and degradation pathways have been studied and are well understood. Impurities are controlled using a risk based control strategy that is based on process knowledge and process characterization.

Drug substance specifications were proposed as per ICH guidelines when applicable. Acceptance criteria are proposed primarily based on the manufacturing process capability, batch analysis data from the 27 batches produced using the proposed commercial process and considering the relevance to the clinical safety and efficacy. Impurities are controlled at the levels lower than what have been qualified in the toxicology studies. Controls of potential genotoxic impurities use a risk based approach instead of regular controls applied to the genotoxic impurities (b) (4) µg/day), considering the API is potentially genotoxic and patient population being advanced breast cancer patients. Impurity controls have been discussed with the pharm/tox reviewer, Dr. Wei Chen.

Drug substance stability studies demonstrated that palbociclib is physicochemically stable under both long term 25°C/60%RH (12 months) and accelerated 40°C/75%RH (6 months) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that palbociclib is not light sensitive. Forced degradation study has established that the HPLC method for purity is stability indicating. The proposed retest date of (b) (4) months stored (b) (4) is acceptable.

The proposed comparability protocol to (b) (4) (b) (4) of the drug substance synthesis. Pfizer plans to (b) (4). Pfizer plans to submit a CBE30 supplement to provide data obtained per the comparability protocol. The proposed comparability protocol is acceptable.

(2) Drug Product

Ibrance (palbociclib) Capsules are available in 75 mg, 100 mg and 125 mg dosage strengths. The capsules contain palbociclib (a free base) as the active pharmaceutical ingredient together with microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin opaque capsule shells (with composition of gelatin, red iron oxide, yellow iron oxide, and titanium dioxide) and print ink. All three strengths of palbociclib capsules are formulated (b) (4) in the three strengths, except for the capsule shells.

Ibrance (palbociclib) Capsules are available for oral administration in three strengths: a 75 mg capsule (Size #2, light orange body/ light orange cap) in which the body is printed with "PBC 75" and the cap printed with "Pfizer" in white; a 100 mg capsule (Size #1, light orange body/caramel cap) in which the body is printed with "PBC 100" and the cap printed with "Pfizer" in white; and a 125 mg capsule (Size # 0, caramel body/caramel cap) in which the body is printed with "PBC 125" and the cap printed with "Pfizer" in white. Ibrance (palbociclib) Capsules are supplied in 60 ml HDPE bottles of 21 capsules for all three strengths.

Executive Summary Section

Formulation development of Ibrance (palbociclib) Capsules was performed by Pfizer through two sites: Groton, CT, US and Freiburg, Germany. The basic steps in the manufacturing process consist of (b) (4)

(b) (4). Standard release specifications for a solid oral dosage form have been proposed. Pfizer Manufacturing Deutschland GmbH in Freiburg, Germany is the proposed commercial site for the drug product manufacturing, testing, packaging, and labeling; while Pfizer Pharmaceuticals LLC in Vega Baja, Puerto Rico and Pharmacia and Upjohn Co (A subsidiary of Pfizer Inc) in Kalamazoo, MI are the proposed sites for (b) (4) packaging and labeling.

The applicant submitted the stability data from three primary registration batches for each of 75 mg strength, 100 mg strength, and 125 mg strength capsules up to 12 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the drug product in all three strengths packaged in HDPE bottles and stored at controlled room temperature. The submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

A clear relationship was established between the configuration of the (b) (4) and the drug product quality attribute - (b) (4), through the registration stability and clinical supply manufacturing campaigns. This relationship resulted in the modification of (b) (4)

(b) (4) This change is well supported by the (b) (4) content uniformity data (by assay) and dissolution data (refer to Dr. Minerva Hughes' Biopharm review) collected across each entire batch during the (b) (4) process for 17 batches which are at either registration batch size scales or full commercial batch scales. The correlation between the (b) (4) and (b) (4) content uniformity (by assay) has been well established through these bridging studies. These studies demonstrate that there is no impact from the (b) (4) process change to the drug product content uniformity which directly links to dose accuracy for clinical efficacy and safety. In addition, the impact from this change on other stability indicating quality attributes (appearance, assay, degradation products, and (b) (4)) would be extremely low. Therefore, the stability data obtained from the primary registration stability study support the shelf life for the marketed drug product. For additional information, refer to Biopharm review by Dr. Minerva Hughes for dissolution assessment from the (b) (4) process change.

B. Description of How the Drug Product is Intended to be Used

Ibrance is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

The recommended dose of IBRANCE is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE should



CHEMISTRY REVIEW



Executive Summary Section

be taken with food in combination with letrozole 2.5 mg once daily given continuously. Dose modification of IBRANCE is recommended based on individual safety and tolerability.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. The Biopharm reviewer has completed the quality assessment and found and the drug product is acceptable from the biopharmaceutics prospective.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Ibrance.

Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert were incorporated into the revised labeling for the labeling meeting of the NDA on 13-Jan-2015. The revised container labels, as amended by the applicant on 13-Jan-2015 are acceptable from the CMC perspective.

The Office of Compliance issued an overall "acceptable" recommendation dated 30-Nov-2014 for all facilities used for manufacturing and control of the drug substance.

III. Administrative

A. Reviewer's Signature

Joyce
Crich -S

Digitally signed by Joyce Crich -S
DN: c=US, o=U.S. Government,
ou=FDA, ou=People,
cn=Joyce Crich -S,
0.9.2342.19200300.100.1.1=30058728
2
Date: 2015.01.14 02:55:48 -05'00'

Xiaohong
Chen -A

Digitally signed by Xiaohong Chen -A
DN: c=US, o=U.S. Government, ou=HHS,
ou=FDA, ou=People, cn=Xiaohong Chen
-A,
0.9.2342.19200300.100.1.1=1300133168
Date: 2015.01.14 11:11:51 -05'00'

Branch Chief's Signature

B. Endorsement Block

Reviewer Name/Date: Joyce Crich, Ph.D (for drug product)
Xiao H Chen, Ph.D (for drug substance)

Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

Amy Tilley/OHOP/DOP1/Regulatory PM
Haripada Sarker /ONDQA/CMC Lead
Teicher Agosto/ONDQA/PM
Ali Al Hakim/ONDQA/DNDQA I/Branch Chief
Ramesh Sood/ONDQA/DNDQA I Acting Director

Ali H. Al-
Hakim -S

Digitally signed by Ali H. Al-
Hakim -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.19200300.100.1.1=130
0093815, cn=Ali H. Al- Hakim -S
Date: 2015.01.14 11:19:53
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NDA 207-103

**Ibrance (palbociclib) Capsules,
75, 100, and 125 mg**

Pfizer, Inc.

Drug Product Section of Team Review

Joyce Crich, Ph.D.
Review Chemist

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I
Branch II**

**Chemistry, Manufacturing, and Controls (CMC)
For the Division of Hematology Products**

Table of Contents

Table of Contents	2
Chemistry Review Data Sheet.....	4
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable.....	9
II. Summary of Chemistry Assessments	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative.....	12
A. Reviewer's Signature.....	12
B. Endorsement Block.....	12
C. CC Block	12
Chemistry Assessment	13
I. Review Of Common Technical Document-Quality (Ctd-Q) Module 3.2: Body Of Data.....	13
S DRUG SUBSTANCE.....	13
P DRUG PRODUCT	13
P.1 Description and Composition of the Drug Product	13
P.2 Pharmaceutical Development.....	17
P.3 Manufacture	61
P.4 Control of Excipients	66
P.5 Control of Drug Product.....	72
P.6 Reference Standards or Materials.....	103
P.7 Container Closure System	103
P.8 Stability	106
A APPENDICES	124
A.1 Facilities and Equipment (biotech only).....	124
A.2 Adventitious Agents Safety Evaluation.....	124
A.3 Novel Excipients	125
R REGIONAL INFORMATION	125
R1 Executed Batch Records.....	125
R2 Comparability Protocols.....	125
R3 Methods Validation Package	130

II. Review of Common Technical Document-Quality (Ctd-Q) Module 1	131
A. Labeling & Package Insert.....	131
B. Environmental Assessment or Claim of Categorical Exclusion	133
III. List of Deficiencies to be Communicated.....	134

Executive Summary Section

Chemistry Review Data Sheet

1. NDA 207-103

2. REVIEW #: 1

3. REVIEW DATE: 31-Dec-2014

4. REVIEWER: Joyce Crich, Ph.D

5. PREVIOUS DOCUMENTS:

Previous Documents

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Type B Pre-NDA Meeting (28-Feb-2014) Minutes

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Executive Summary Section

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Name: Pfizer, Inc
Address: 235 East 42nd Street, New York, NY 10017
Representative: N/A
Telephone: (212) 733-2323

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Ibrance®
b) Non-Proprietary Name (USAN): palbociclib
c) Code Name/# (ONDC only): PXD101
d) Chem. Type/Submission Priority (ONDC only):
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: 505(b)(1)

10. PHARMACOL. CATEGORY: small molecule inhibitor of CDK 4 and 6
for the treatment of advanced breast cancer

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 75 mg, 100 mg and 125 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: ☒ Rx ☐ OTC15. [SPOTS \(SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM\):](#)

☐ SPOTS product – Form Completed

☒ Not a SPOTS product

Executive Summary Section

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): palbociclib

Name (CAS): pyrido[2,3-*d*]pyrimidin-7(8*H*)-one, 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2-pyridinyl]amino]-

IUPAC Name: 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino}pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

Other Name: *N*-hydroxy-3-(3-phenylsulphamoylphenyl) acrylamide

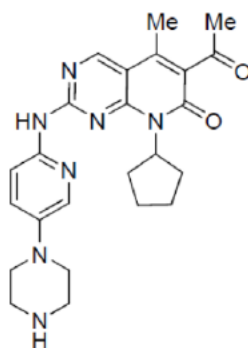
Company code: PXD101

(CAS) Registry Number: 414864-00-9, 866323-14-0

Mol. Formula: C₂₄H₂₉N₇O₂

Mol. Wt.: 447.54 g/mole

Structural Formula:



Executive Summary Section

17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		See sections 1.4.1, 3.2.P.1 and 3.2.P.4
	IV		(b) (4)	4	Adequate		See sections 1.4.1, 3.2.P.1 and 3.2.P.4
	III		(b) (4)	4	Adequate		See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III		(b) (4)	3 & 4	Adequate	20-May-2010 (by Dr. Y. Zhang)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III		(b) (4)	3 & 4	Adequate	04-Feb-2014 (by Dr. Y-C Chen)	See sections 1.4.1 & 3.2.P.7
	III		(b) (4)	3 & 4	Adequate	04-Feb-2014 (by Dr. X. Li)	See sections 1.4.1. & 3.2.P.7
	III		(b) (4)	3 & 4	Adequate	25-Sep-2014 (by Dr. R. Frankewich)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III		(b) (4)	3 & 4	Adequate	21-Mar-2012 (by Dr. G. Holbert)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7

¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 –Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

Executive Summary Section

B. Other Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	69324	Pfizer, Inc.	Palbociclib (PD-0332991)

18. STATUS:

ONDC:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-Nov-2014	
Pharm/Tox	Degradation Products in Drug Product are acceptable*	See DARRTS for review*	Wei Chen
Biopharm	Pending	See Panorama for review	Minerva Hughes
LNC	N/A		
Methods Validation**	Pending		
DMEPA***	The proposed proprietary name, Ibrance is acceptable	05-Sep-2014	Mathew Davis
EA	Categorical exclusion (see review)	29-Dec-2014	Joyce Crich
Microbiology	Approval from microbiology product quality standpoint	08-Dec-2014	Jessica Cole

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewer in her 30-Sep-2014 e-mail that the acceptance criterion for the degradation product (b) (4) in the drug product is qualified. See Section 3.2.P.5.6 for detailed information.

*Methods validation consult was sent to the FDA St. Louis Laboratory on 17-Sep-2014. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

***DMEPA: Division of Medication Error Prevention and Analysis

Executive Summary Section

The Chemistry Review for NDA 207-103

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is approvable pending satisfactory Biopharm recommendation.

Expiry Dating Recommendation

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (75 mg, 100 mg, and 125 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

B. Recommendation on Phase 4 (Post-Marketing) Commitments, Agreements, and/or Risk Management Steps, if Approvable

None

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

(1) Drug Substance

The chemical name for palbociclib is 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]-phenyl]-, (2*E*)-. Palbociclib has a molecular formula of C₂₄H₂₉N₇O₂ and a molecular weight of 447.54 Da. Palbociclib is a yellow to orange powder with pK_a of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly. Palbociclib is (b) (4) and requires (b) (4).

The (b) (4) of palbociclib was selected for development. Two other forms were identified during development ((b) (4)). No (b) (4) was found. (b) (4)

Palbociclib is manufactured by a (b) (4). Justification for the proposed starting materials is provided based on the discussion and the FDA comments at the EOP-2 meeting. Throughout the development the synthetic route (b) (4)

ater in the development, (b) (4)

. The proposed commercial process

Executive Summary Section

(b) (4) has been used to manufacture up to 27 batches for clinical supply including the pivotal clinical studies. (b) (4) have been studied and are well understood. Impurities are controlled using a risk based control strategy that is based on process knowledge and process characterization.

Drug substance specifications were proposed as per ICH guidelines when applicable. Acceptance criteria are proposed primarily based on the manufacturing process capability, batch analysis data from the 27 batches produced using the proposed commercial process and considering the relevance to the clinical safety and efficacy. Impurities are controlled at the levels lower than what have been qualified in the toxicology studies. Controls of potential genotoxic impurities use a risk based approach instead of regular controls applied to the genotoxic impurities ((b) (4) µg/day), considering the API is potentially genotoxic and patient population being advanced breast cancer patients. Impurity controls have been discussed with the pharm/tox reviewer, Dr. Wei Chen.

Drug substance stability studies demonstrated that palbociclib is physicochemically stable under both long term 25°C/60%RH (12 months) and accelerated 40°C/75%RH (6 months) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that palbociclib is not light sensitive. Forced degradation study has established that the HPLC method for purity is stability indicating. The proposed retest date of (b) (4) months stored (b) (4) is acceptable.

The proposed comparability protocol to (b) (4) (b) (4) of the drug substance synthesis. Pfizer plans to (b) (4). Pfizer plans to submit a CBE30 supplement to provide data obtained per the comparability protocol. The proposed comparability protocol is acceptable.

(2) Drug Product

Ibrance (palbociclib) Capsules are available in 75 mg, 100 mg and 125 mg dosage strengths. The capsules contain palbociclib (a free base) as the active pharmaceutical ingredient together with microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin opaque capsule shells (with composition of gelatin, red iron oxide, yellow iron oxide, and titanium dioxide) and print ink. All three strengths of palbociclib capsules are formulated (b) (4) in the three strengths, except for the capsule shells.

Ibrance (palbociclib) Capsules are available for oral administration in three strengths: a 75 mg capsule (Size #2, light orange body/ light orange cap) in which the body is printed with "PBC 75" and the cap printed with "Pfizer" in white; a 100 mg capsule (Size #1, light orange body/caramel cap) in which the body is printed with "PBC 100" and the cap printed with "Pfizer" in white; and a 125 mg capsule (Size # 0, caramel body/caramel cap) in which the body is printed with "PBC 125" and the cap printed with "Pfizer" in white. Ibrance (palbociclib) Capsules are supplied in 60 ml HDPE bottles of 21 capsules for all three strengths.

Executive Summary Section

Formulation development of Ibrance (palbociclib) Capsules was performed by Pfizer through two sites: Groton, CT, US and Freiburg, Germany. The basic steps in the manufacturing process consist of (b) (4)

(b) (4). Standard release specifications for a solid oral dosage form have been proposed. Pfizer Manufacturing Deutschland GmbH in Freiburg, Germany is the proposed commercial site for the drug product manufacturing, testing, packaging, and labeling; while Pfizer Pharmaceuticals LLC in Vega Baja, Puerto Rico and Pharmacia and Upjohn Co (A subsidiary of Pfizer Inc) in Kalamazoo, MI are the proposed sites for (b) (4) packaging and labeling.

The applicant submitted the stability data from three primary registration batches for each of 75 mg strength, 100 mg strength, and 125 mg strength capsules up to 12 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the drug product in all three strengths packaged in HDPE bottles and stored at controlled room temperature. The submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

A clear relationship was established between the configuration of the (b) (4) and the drug product quality attribute - (b) (4), through the registration stability and clinical supply manufacturing campaigns. This relationship resulted in the modification of (b) (4)

(b) (4). This change is well supported by the (b) (4) content uniformity data (by assay) and dissolution data (refer to Dr. Minerva Hughes' Biopharm review) collected across each entire batch during the (b) (4) process for 17 batches which are at either registration batch size scales or full commercial batch scales. The correlation between the (b) (4) and (b) (4) content uniformity (by assay) has been well established through these bridging studies. These studies demonstrate that there is no impact from the (b) (4) process change to the drug product content uniformity which directly links to dose accuracy for clinical efficacy and safety. In addition, the impact from this change on other stability indicating quality attributes (appearance, assay, degradation products, and (b) (4)) would be extremely low. Therefore, the stability data obtained from the primary registration stability study support the shelf life for the marketed drug product. For additional information, refer to Biopharm review by Dr. Minerva Hughes for dissolution assessment from the (b) (4) process change.

B. Description of How the Drug Product is Intended to be Used

Ibrance is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

The recommended dose of IBRANCE is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. IBRANCE should



CHEMISTRY REVIEW



Executive Summary Section

be taken with food in combination with letrozole 2.5 mg once daily given continuously. Dose modification of IBRANCE is recommended based on individual safety and tolerability.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. However, the final decision on the acceptability from the overall quality prospective is pending the assessment of Biopharm review by Dr. Minerva Hughes.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Ibrance.

Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert will be incorporated into the revised labeling for the labeling meeting of the NDA on 13-Jan-2015. Any projected revised container labels from the applicant will be reviewed from the CMC perspective.

The Office of Compliance issued an overall "acceptable" recommendation dated 30-Nov-2014 for all facilities used for manufacturing and control of the drug substance.

III. Administrative

A. Reviewer's Signature

Joyce
Crich -S

Digitally signed by Joyce Crich -S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
cn=Joyce Crich -S,
0.9.2342.1.1200000.100.1.1=2000
387293
Date: 2015.01.04 21:59:19 -0500

Branch Chief's Signature

Ali H. Al-
Hakim -S

Digitally signed by Ali H. Al-Hakim
-S
DN: c=US, o=U.S. Government,
ou=HHS, ou=FDA, ou=People,
0.9.2342.1.1200000.100.1.1=13000
93815, cn=Ali H. Al-Hakim -S
Date: 2015.01.04 22:14:38 -0500

B. Endorsement Block

Reviewer Name/Date: Joyce Crich, Ph.D.
Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

Amy Tilley/OHOP/DOP1/Regulatory PM
Haripada Sarker /ONDQA/CMC Lead
Teicher Agosto/ONDQA/PM
Ali Al Hakim/ONDQA/DNDQA I/Branch Chief
Ramesh Sood/ONDQA/DNDQA I Acting Director

NDA 207-103

**Ibrance (palbociclib) Capsules,
75, 100, and 125 mg**

Pfizer, Inc.

Drug Substance Section of Team Review

Xiao-Hong Chen, Ph.D.

**Office of New Drug Quality Assessment
Division of New Drug Quality Assessment I**

CMC Review of NDA 207-103

For the Division of Drug Oncology Products I

Table of Contents

Table of Contents	2
The Executive Summary	9
I. Recommendations	9
A. Recommendation and Conclusion on Approvability	9
B. Recommendation on Post Marketing Requirements, Post Marketing Commitments, Agreements, and/or Risk Management Steps, if Approvable.	9
II. Summary of Chemistry Assessments	9
A. Description of the Drug Product(s) and Drug Substance(s)	9
B. Description of How the Drug Product is Intended to be Used.....	11
C. Basis for Approvability or Not-Approval Recommendation.....	12
III. Administrative	12
A. Reviewer's Signature	12
See appended electronic signature page.	12
B. Endorsement Block.....	12
D. CC Block.....	Error! Bookmark not defined.
I. Review of CTD - Module 3: Quality: Body Of Data	14
S DRUG SUBSTANCE.....	14
S.1 General Information.....	14
S.2 Manufacture	15
S.3 Characterization	50
S.4 Control of Drug Substance.....	57
S.5 Reference Standards or Materials	79
S.6 Container Closure System.....	79
S.7 Stability	79
P DRUG PRODUCT.....	86
A APPENDICES	86
A.1 Facilities and Equipment (biotech only).....	86
A.2 Adventitious Agents Safety Evaluation.....	86
A.3 Novel Excipients	86
R REGIONAL INFORMATION	86
R1 Executed Batch Records.....	86

R2 Comparability Protocols.....	86
R3 Methods Validation Package	90
II. Review Of Common Technical Document-Quality (CTD-Q) Module 1	90
A. Labeling & Package Insert.....	90
B. Environmental Assessment Or Claim Of Categorical Exclusion	90
III. List of Deficiencies/Comments To Be Communicated	90

Chemistry Review Data Sheet

1. NDA 207-103
2. REVIEW #1:
3. REVIEW DATE: 22-Dec-2014
4. REVIEWER: Xiao-Hong Chen, Ph.D.
5. PREVIOUS DOCUMENTS:

<u>Previous Documents</u>	<u>Document Date</u>
Original IND 69,324 submission	10-Mar-2004
CMC only Pre-NDA Meeting (23-Jan-2014) Minutes	11-Feb-2014
Type B Pre-NDA Meeting (28-Feb-2014) Minutes	31-Mar-2014

6. SUBMISSION(S) BEING REVIEWED:

<u>Submission(s) Reviewed</u>	<u>Document Date</u>
Rolling NDA submission	30-Jun-2013
Original NDA submission	13-Aug-2013
Amendment SN0042	19-Nov-2014
Amendment SN0048	26-Nov-2014
Amendment SN0053	08-Dec-2014
Amendment SN0059	26-Nov-2014
Amendment SN0061	08-Dec-2014

7. NAME & ADDRESS OF APPLICANT:

NAME:	Pfizer, Inc.
ADDRESS:	235 East 42nd Street New York, NY 10017
REPRESENTATIVE:	N/A.

TELEPHONE:

(212) 733-2323

8. DRUG PRODUCT NAME/CODE/TYPE:

- a) Proprietary Name: Ibrance®
- b) Non-Proprietary Name (USAN): palbociclib
- c) Code Name/#: PXD101
- d) Chem. Type/Submission Priority:
 - Chem. Type: 1
 - Submission Priority: P

9. LEGAL BASIS FOR SUBMISSION: Filed 505(b)(1)

10. PHARMACOL. CATEGORY: small molecule inhibitor of CDK 4 and 6 for treatment of patients with advanced breast cancer

11. DOSAGE FORM: Capsules

12. STRENGTH/POTENCY: 75 mg, 100 mg and 125 mg

13. ROUTE OF ADMINISTRATION: Oral

14. Rx/OTC DISPENSED: X Rx OTC

15. **SPOTS (SPECIAL PRODUCTS ON-LINE TRACKING SYSTEM):**

 SPOTS product – Form Completed

 X Not a SPOTS product

16. CHEMICAL NAME, STRUCTURAL FORMULA, MOLECULAR FORMULA, MOLECULAR WEIGHT:

Name (USAN, INN): palbociclib

Name (CAS): pyrido[2,3-*d*]pyrimidin-7(8*H*)-one, 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2-pyridinyl]amino]-

IUPAC Name: 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(piperazin-1-yl)pyridin-2-yl]amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one

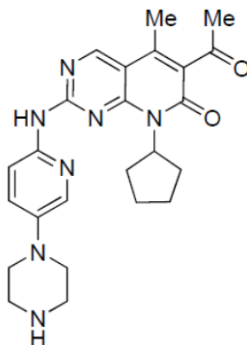
Other Name: *N*-hydroxy-3-(3-phenylsulphamoylphenyl) acrylamide
 Company code: PXD101

(CAS) Registry Number: 414864-00-9, 866323-14-0

Mol. Formula: $C_{24}H_{29}N_7O_2$

Mol. Wt.: 447.54 g/mole

Structural Formula:



17. RELATED/SUPPORTING DOCUMENTS:

A. DMFs:

DMF #	Type	Holder	Item Referenced	Code ¹	Status ²	Date Review Completed	Comments
(b) (4)	IV	(b) (4)	(b) (4)	4	Adequate		See sections 1.4.1 and 3.2.P.4
	IV			4	Adequate		See sections 1.4.1, 3.2.P.1 and 3.2.P.4
	III			4	Adequate		See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III			3 & 4	Adequate	20-May-2010 (by Dr. Y. Zhang)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
	III			3 & 4	Adequate	04-Feb-2014 (by Dr. Y-C Chen)	See sections 1.4.1 & 3.2.P.7
	III			3 & 4	Adequate	04-Feb-2014 (by Dr. X. Li)	See sections 1.4.1. & 3.2.P.7
	III			3 & 4	Adequate	25-Sep-2014 (by Dr. R. Frankewich)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7

(b) (4)	III	(b) (4)	3 & 4	Adequate	21-Mar-2012 (by Dr. G. Holbert)	See sections 1.4.1, 3.2.P.2.4 and 3.2.P.7
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¹ Action codes for DMF Table:

1 – DMF Reviewed.

Other codes indicate why the DMF was not reviewed, as follows:

2 – Type 1 DMF

3 – Reviewed previously and no revision since last review

4 – Sufficient information in application

5 – Authority to reference not granted

6 – DMF not available

7 – Other (explain under "Comments")

² Adequate, Inadequate, or N/A (There is enough data in the application, therefore the DMF did not need to be reviewed)

B. Other Supporting Documents:

Doc #	OWNER	ITEM REFERENCED	STATUS	DATE REVIEW COMPLETED	COMMENTS

C. Related Documents:

DOCUMENT	APPLICATION NUMBER	OWNER	DESCRIPTION/COMMENT
IND	69324	Pfizer, Inc.	Original IND submitted on 10-Mar-2004.

18. CONSULTS/CMC-RELATED REVIEWS:

CONSULTS/ CMC RELATED REVIEWS	RECOMMENDATION	DATE	REVIEWER
Biometrics	N/A		
EES	Acceptable	30-Nov-2014	
Pharm/Tox	Impurities qualification in drug substance is acceptable.	See DARRTS for review*	Wei Chen, Ph.D
Biopharm	Pending	See	Minerva Hughes, Ph.D

		Panorama for review	
LNC	N/A		
Methods Validation*	Pending		
DMEPA**	The proposed proprietary name, Ibrance is acceptable	05-Sep-2014	Mathew Davis
EA	Categorical exclusion (see review)	29-Dec-2014	Joyce Crich, Ph.D
Microbiology	Approval from microbiology product quality standpoint	08-Dec-2014	Jessica Cole, Ph.D

*Dr. Wei Chen, the pharm/tox reviewer for this NDA, informed the CMC reviewer in her 20-Nov-2014 e-mail that the acceptance criteria for the drug substance impurities (b) (4) are acceptable from a pharmacology/toxicology perspective based on the nonclinical data and proposed indication. See Section 3.2.S.4.5 for detailed information.

*Methods validation consult was sent to the FDA St. Louis Laboratory on 17-Sep-2014. See DARRTS for the consult request. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

***DMEPA: Division of Medication Error Prevention and Analysis

The Chemistry Review for NDA 207-103

The Executive Summary

I. Recommendations

A. Recommendation and Conclusion on Approvability

From the chemistry, manufacturing and controls standpoint, this NDA is approvable pending satisfactory Biopharm recommendation.

Expiry Dating Recommendation

Based on the provided stability data, a 24-month expiration dating period is granted for the drug product (75 mg, 100 mg, and 125 mg) when stored at USP controlled room temperature 20-25°C (68-77°F); excursions permitted to 15-30°C (59-86°F).

B. Recommendation on Post Marketing Requirements, Post Marketing Commitments, Agreements, and/or Risk Management Steps, if Approvable.

N/A.

II. Summary of Chemistry Assessments

A. Description of the Drug Product(s) and Drug Substance(s)

Drug Substance

The chemical name for palbociclib is 2-Propenamide, *N*-hydroxy-3-[3-[(phenylamino)sulfonyl]-phenyl]-, (2*E*)-. Palbociclib has a molecular formula of C₂₄H₂₉N₇O₂ and a molecular weight of 447.54 Da. Palbociclib is a yellow to orange powder with pKa of 7.4 (the secondary piperazine nitrogen) and 3.9 (the pyridine nitrogen). At or below pH 4, palbociclib behaves as a high-solubility compound. Above pH 4, the solubility of the drug substance reduces significantly. Palbociclib is (b) (4) and requires (b) (4).

The (b) (4) of palbociclib was selected for development. Two other forms were identified during development ((b) (4)). No (b) (4) was found. (b) (4) (u) (4)

Palbociclib is manufactured by a (b) (4). Justification for the proposed starting materials is provided based on the discussion and the FDA comments at the EOP-2 meeting. Throughout the development the synthetic route (b) (4)

Later in the development, (u) (4)

. The proposed commercial process

(b) (4) has been used to manufacture up to 27 batches for clinical supply including the pivotal clinical studies. Impurities formation during manufacturing and degradation pathways have been studied and are well understood. Impurities are controlled using a risk based control strategy that is based on process knowledge and process characterization.

Drug substance specifications were proposed as per ICH guidelines when applicable. Acceptance criteria are proposed primarily based on the manufacturing process capability, batch analysis data from the 27 batches produced using the proposed commercial process and considering the relevance to the clinical safety and efficacy. Impurities are controlled at the levels lower than what have been qualified in the toxicology studies. Controls of potential genotoxic impurities use a risk based approach instead of regular controls applied to the genotoxic impurities ((b) (4) µg/day), considering the API is potentially genotoxic and patient population being advanced breast cancer patients. Impurity controls have been discussed with the pharm/tox reviewer, Dr. Wei Chen.

Drug substance stability studies demonstrated that palbociclib is physicochemically stable under both long term 25°C/60%RH (12 months) and accelerated 40°C/75%RH (6 months) conditions. No significant change or trending has been observed under either storage conditions. Photostability showed that palbociclib is not light sensitive. Forced degradation study has established that the HPLC method for purity is stability indicating. The proposed retest date of (b) (4) months stored (b) (4) is acceptable.

The proposed comparability protocol to qualify a process change to (b) (4) of the drug substance synthesis. Pfizer plans to (b) (4). Pfizer plans to submit a CBE30 supplement to provide data obtained per the comparability protocol. The proposed comparability protocol is acceptable.

Drug Product

Ibrance (palbociclib) Capsules are available in 75 mg, 100 mg and 125 mg dosage strengths. The capsules contain palbociclib (a free base) as the active pharmaceutical ingredient together with microcrystalline cellulose, lactose monohydrate, sodium starch glycolate, colloidal silicon dioxide, magnesium stearate, and hard gelatin opaque capsule shells (with composition of gelatin, red iron oxide, yellow iron oxide, and titanium dioxide) and print ink. All three strengths of palbociclib capsules are formulated (b) (4) in the three strengths, except for the capsule shells.

Ibrance (palbociclib) Capsules are available for oral administration in three strengths: a 75 mg capsule (Size #2, light orange body/ light orange cap) in which the body is printed with "PBC 75" and the cap printed with "Pfizer" in white; a 100 mg capsule (Size #1, light orange body/caramel cap) in which the body is printed with "PBC 100" and the cap printed with "Pfizer" in white; and a 125 mg capsule (Size # 0, caramel body/caramel cap) in which the body is printed with "PBC 125" and the cap printed with "Pfizer" in white. Ibrance (palbociclib) Capsules are supplied in 60 ml HDPE bottles of 21 capsules for all three strengths.

Formulation development of Ibrance (palbociclib) Capsules was performed by Pfizer through two sites: Groton, CT, US and Freiburg, Germany. The basic steps in the manufacturing process consist of (b) (4)

(b) (4) Standard release specifications for a solid oral dosage form have been proposed. Pfizer Manufacturing Deutschland GmbH in Freiburg, Germany is the proposed commercial site for the drug product manufacturing, testing, packaging, and labeling; while Pfizer Pharmaceuticals LLC in Vega Baja, Puerto Rico and Pharmacia and Upjohn Co (A subsidiary of Pfizer Inc.) in Kalamazoo, MI are the proposed sites for (b) (4) packaging and labeling.

The applicant submitted the stability data from three primary registration batches for each of 75 mg strength, 100 mg strength, and 125 mg strength capsules up to 12 months at 25°C/60% RH and 30°C/75% RH, and up to 6 months at 40°C/75% RH in the primary stability container closure system. Those stability data support the proposed 24 months shelf-life for the drug product in all three strengths packaged in HDPE bottles and stored at controlled room temperature. The submitted photostability study results on the primary lots indicate that the drug product does not require protection from light.

A clear relationship was established between the configuration of the (b) (4) and the drug product quality attribute - (b) (4), through the registration stability and clinical supply manufacturing campaigns. This relationship resulted in the modification of (b) (4)

(b) (4). This change is well supported by the (b) (4) (b) (4) content uniformity data (by assay) and dissolution data (refer to Dr. Minerva Hughes' Biopharm review) collected across each entire batch during the (b) (4) process for 17 batches which are at either registration batch size scales or full commercial batch scales. The correlation between the (b) (4) and (b) (4) content uniformity (by assay) has been well established through these bridging studies. These studies demonstrate that there is no impact from the (b) (4) process change to the drug product content uniformity which directly links to dose accuracy for clinical efficacy and safety. In addition, the impact from this change on other stability indicating quality attributes (appearance, assay, degradation products, and (b) (4)) would be extremely low. Therefore, the stability data obtained from the primary registration stability study support the shelf life for the marketed drug product. For additional information, refer to Biopharm review by Dr. Minerva Hughes for dissolution assessment from the (b) (4) process change.

B. Description of How the Drug Product is Intended to be Used

Ibrance is indicated in combination with letrozole for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease.

The recommended dose of Ibrance is a 125 mg capsule taken orally once daily for 21 consecutive days followed by 7 days off treatment to comprise a complete cycle of 28 days. Ibrance should be taken with food in combination with letrozole 2.5 mg once daily given continuously. Dose modification of IBRANCE is recommended based on individual safety and tolerability.

C. Basis for Approvability or Not-Approval Recommendation

Adequate data have been provided for the manufacture and controls of the drug substance and drug product. The microbiology reviewer has determined that the drug product is acceptable from the microbiology perspective. However, the final decision on the acceptability from the overall quality prospective is pending the assessment of Biopharm review by Dr. Minerva Hughes.

The Division of Medication Error Prevention and Analysis (DMEPA) has no objections to the use of the proposed proprietary name Ibrance.

Methods validation consult was sent to the FDA St. Louis Laboratory for the drug substance and drug product analysis. Methods validation has not been completed by the FDA laboratory but is not required for approval of the NDA.

The CMC revisions of the package insert will be incorporated into the revised labeling for the labeling meeting of the NDA on 13-Jan-2015. Any projected revised container labels from the applicant will be reviewed from the CMC perspective.

The Office of Compliance issued an overall "acceptable" recommendation dated 30-Nov-2014 for all facilities used for manufacturing and control of the drug substance.

III. Administrative

A. Reviewer's Signature

Xiaohong Chen -A

Digitally signed by Xiaohong Chen -A
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA, ou=People,
cn=Xiaohong Chen -A, 0.9.2342.19200300.100.1.1=1300133168
Date: 2015.01.06 16:25:45 -05'00'

Branch Chief's Signature

Ali H. Al- Hakim -

S

Digitally signed by Ali H. Al- Hakim -S
DN: c=US, o=U.S. Government, ou=HHS, ou=FDA,
ou=People,
0.9.2342.19200300.100.1.1=1300093815, cn=Ali H.
Al- Hakim -S
Date: 2015.01.06 22:36:54 -05'00'

See appended electronic signature page.

B. Endorsement Block

Reviewer Name/Date: Xiao-Hong Chen, Ph.D.
Branch Chief Name/Date: Ali Al Hakim, Ph.D.

C. CC Block

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immediately following this page

Amy Tilley/OHOP/DOP1/Regulatory PM
Haripada Sarker /ONDQA/CMC Lead
Teicher Agosto/ONDQA/PM
Ali Al Hakim/ONDQA/DNDQA I/Branch Chief
Ramesh Sood/ONDQA/DNDQA I Acting Director

Initial Manufacturing (CGMP/Facilities) Assessment (IMA) and Filing Review for Pre- Marketing Applications (Original)

- I. Review Cover Sheet
- II. Application Detail
- III. Filing Checklist
- IV. Manufacturing Summary
- V. Overall Conclusions and Recommendations

I. Review Cover Sheet

1. OMPQ Reviewer: Robert H. Wittorf, PharmD.

2. NDA/BLA Number: NDA 207103

Submission Date: 13-Aug-2014

21st C. Review Goal Date: TBD

PDUFA Goal Date: 10-Apr-2015

3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	(b) (4)
Established or Non-Proprietary Name (USAN) and strength:	Palbociclib
Dosage Form:	CHG

4. SUBMISSION PROPERTIES:

Review Priority :	Expedited
Applicant Name:	Pfizer, Inc.
Responsible Organization (OND Division):	DOP

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

II. Application Detail

1. INDICATION: Advanced Breast Cancer
2. ROUTE OF ADMINISTRATION: Oral Dosage
3. STRENGTH/POTENCY: Two strengths: 75 mg, 100 mg, and 125 mg
4. Rx/OTC DISPENSED: X☐Rx ☐OTC
5. ELECTRONIC SUBMISSION (yes/no)? Yes
6. PRIORITY CONSIDERATIONS:

	Parameter	Yes	No	Unk	Comment
1.	NME / PDUFA V	X			
2.	Breakthrough Therapy Designation	X			Six month review PDUFA date: 10-Apr-2015
3.	Orphan Drug Designation		X		
4.	Unapproved New Drug		X		
5.	Medically Necessary Determination		X		
6.	Potential Shortage Issues [either alleviating or non-approval may cause a shortage]		X		
7.	Rolling Submission	X			Final portion of rolling submission provided on 13-Aug-2014
8.	Drug/device combination product with consult		X		
9.	Complex manufacturing		X		Capsule Formulation with > ^(b) ₍₄₎ % drug load
10.	Other (e.g., expedited for an unlisted reason)				

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

III. FILING CHECKLIST

The following parameters are necessary in order to initiate a full review (i.e., the application is complete enough to start review but may have deficiencies). On **initial** review of the NDA application:

A. COMPLETENESS OF FACILITY INFORMATION				
	Parameter	Yes	No	Comment
11.	Is all site information complete (e.g., contact information, responsibilities, address)?	X		
12.	Do all sites indicate they are ready to be inspected (on 356h)?	X		
13.	Is a single comprehensive list of all involved facilities available in one location in the application?	X		Location of facilities provided in the 356h
14.	For testing labs, is complete information provided regarding which specific test is performed at each facility and what stage of manufacturing?	X		
15.	Additional notes (non-filing issue) 1. Are all sites registered or have FEI #?	X		
	2. Do comments in EES indicate a request to participate on inspection(s)?		X	
	3. Is this first application by the applicant?		X	

*If any information regarding the facilities is missing/omitted, communicate to OPS/ONDQA regarding missing information and copy EESQuestions. Notify OMPQ management if problems are not resolved within 3 days and it can be a *potential* filing issue.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

B. DRUG SUBSTANCE (DS) / DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
16.	Have any Comparability Protocols been requested?	X		Two comparability protocols have been submitted. One to qualify 78 Page(s) has been widely relied on by the FDA. (b) (4) of the drug substance is to (b) (4)

IMA CONCLUSION				
	Parameter	Yes	No	Comment
17.	Does this application fit one of the EES Product Specific Categories?	X		
18.	Have EERs been cross referenced against the 356h and product specific profile for accuracy and completion? Have all EERs been updated with final PAI recommendation?		X	EERs still in draft form at this time.
19.	From a CGMP/facilities perspective, is the application fileable? If the NDA is not fileable from a product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.	X		

IV. Manufacturing Summary: Critical Issues and Complexities

Does the submission contain any of the following elements?			
Nanotechnology <input type="checkbox"/>	RTRT Proposal <input type="checkbox"/>	PAT <input type="checkbox"/>	Drug/Device Combo <input type="checkbox"/>
PET <input type="checkbox"/>	Design Space X <input type="checkbox"/>	Continuous Mfg <input type="checkbox"/>	Naturally derived API <input type="checkbox"/>
Other (explain):		Not formally a QbD application, however elements are noted as part of the quality control strategy.	

Manufacturing Highlights				
1. Drug Substance				
	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	Synthetic Small Molecule
Include process flow chart/diagram (see eCTD Section 2.3.S.1)				

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Figure 3.2.S.2.2-1. Manufacturing Process for Palbociclib

(b) (4)



2. Drug Product

	Parameter	Yes	No	Comment
	Is manufacturing process considered complex (e.g., unusual unit operations, innovative manufacturing technology, unusual control strategy)?		X	

Include process flow chart/diagram (see eCTD Section 2.3.P.1)

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

(b) (4)



- 3. Facility-Related Risks (e.g., expected in-process testing not being performed, questionable development, unexplained stability failures, data integrity issues, etc.). Describe any potential 21CFR 211 compliance issues.**

No facility risks are noted at any of the facilities.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

4. Drug Product Facility Inspectional History that could impact the manufacturing of this product.

No inspectional facility concerns noted per FACTS review.

Additional information not covered above

The process has greater than (b)(4)% drug load in an immediate release capsule. Due to recent April 2014 inspectional history with CHG coverage and the breakthrough nature of this product a drug product, pre-approval inspection could be waived based on input from the district per EER processing.

OMPQ Initial Manufacturing (CGMP/Facilities) Assessment and Filing Review
For Pre-Marking Applications

Manufacturing Facilities Chart (generated from 602A DARRTS report and OMPQ macro):

For each EER, indicate PAI recommendation on the Manufacturing Facilities Chart above (e.g., PS, GMP, 10 Day, AC based on file review). This is the recommendation that will be entered into EES. **For PAI, include the reason for the PAI (i.e. PAI Trigger) in the comment section of the facilities chart.**

Establishment Name	EER Creation Date	FEI Num	District Short	Country Code	Responsibilities	Profile Code	Recent Inspection History Dates, Classifications	PAI Recommendation	Most Recent Milestone	Most Recent EER Compliance Status	Comment
PHARMACIA AND UPJOHN COMPANY, DIV. OF PFIZER, NC.	9/9/2014	1810189	DET	USA	Packaging	CHG	(b) (4)	Based on Profile	OC RECOMMENDATION	AC	Re-eval Date: 20-Jun-2017
PFIZER PHARMACEUTICALS LLC	9/9/2014	3002173302	SJN	USA	Packaging	CHG		Based on Profile	OC RECOMMENDATION	AC	Re-eval Date: 16-Jul-2017
PFIZER GMBH	9/9/2014	3002807097	EEU	DEU	Manufacturing and Testing of Drug Product	CHG		Based on Profile	OC RECOMMENDATION	AC	Re-eval Date: 03-Apr-2016
PFIZER IRELAND PHARMACEUTICALS INC.	9/9/2014	3002807852	WEU	IRL	Manufacturing and Testing of Drug Substance	CSN		Waiting on Inspectional Information from District (refer to inspectional dates)	SUBMITTED TO DO	PN	Pending Inspectional Results

V. Overall Conclusions and Recommendations

Is the application fileable? (yes/no, Yes to questions 11-12) Yes
Based on Section IV, is a KTM warranted for any PAI? No If yes, please identify the sites in the above chart.
Are there comments/issues to be included in the 74 day letter, including appropriate identification of facilities? (yes/no) No
Comments for 74 Day Letter
1.
2.
3.

REVIEW AND APPROVAL (DARRTS)

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

ROBERT H WITTORF
10/08/2014

Initial Quality Assessment (IQA) and Filing Review for Pre-Marketing Applications

IQA and Filing Review Cover Sheet

1. NEW DRUG APPLICATION NUMBER: 207103

2. DATES AND GOALS:

Letter Date: 8/13/2014	Submission Received Date : 8/13/2014
PDUFA Goal Date: 2/13/2015 (priority)	

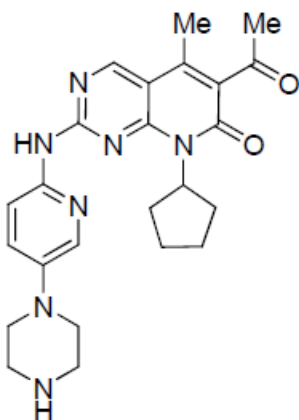
3. PRODUCT PROPERTIES:

Trade or Proprietary Name:	Ibrance
Established or Non-Proprietary Name (USAN):	Palbociclib
Dosage Form:	Capsule
Route of Administration	Oral
Strength/Potency	75 mg, 100 mg, and 125 mg
Rx/OTC Dispensed:	Rx

4. INDICATION: Advanced Breast Cancer (ABC).

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

5. DRUG SUBSTANCE STRUCTURAL FORMULA:



6. NAME OF APPLICANT (as indicated on Form 356h): Pfizer Inc.

7. SUBMISSION PROPERTIES:

Review Priority:	Priority/Standard Review Requested
Submission Classification (Chemical Classification Code):	Type 1 (New Molecular Entity)
Application Type:	505(b)(1)
Breakthrough Therapy	Yes No
Responsible Organization (Clinical Division):	DOP1, OHOP.

8. CONSULTS:

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Biometrics		X	Not applicable
Clinical Pharmacology		X	Not applicable
Establishment Evaluation Request (EER)	X		
Pharmacology/Toxicology		X	Determined by the primary reviewer
Methods Validation	X		
Environmental Assessment		X	Determined by the primary reviewer. Claim of categorical exclusion has been provided.
CDRH		X	Not applicable

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (*CMC and Biopharmaceutics*)**

CONSULT	YES	NO	COMMENTS: (list date of request if already sent)
Other (Micro)	X		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

Overall Filing Conclusions and Recommendations

CMC:

Is the Product Quality Section of the application fileable from a CMC perspective? Yes No
CMC Filing Issues: No
1.

Are there potential CMC review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
CMC Comments for 74-Day Letter: No
1.

Biopharmaceutics:

Is the Product Quality Section of the application fileable from a Biopharmaceutics perspective? Yes No
Biopharmaceutics Filing Issues:
1. None.

Are there potential Biopharmaceutics review issues to be forwarded to the Applicant with the 74-Day letter? Yes No
Biopharmaceutics Comments for 74-Day Letter:
1. None.

Microbiology:

Is the Product Quality Section of the application fileable from a Microbiology perspective? Yes No
Microbiology Filing Issues: no filing issues
See Microbiology Filing Review in DARRTS for details and for any potential Microbiology review issues by Jessica Cole. May have comment for the 74 day letter.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

CMC Summary of Initial Quality Assessment

Does the submission contain any of the following elements?			
Nanotechnology	QbD Elements	PET	Other, please explain
No	Some	No	No

Is a team review recommended?	Yes	No
Suggested expertise for team: Yes		
CMC Reviewer: Joyce Crich, Ph.D. and Xiao Hong Chen, Ph. D.		
Biopharmaceuticals Reviewer: Minerva Hughes, Ph.D.		
Product Quality Microbiology Reviewer: Jessica Cole, Ph.D.		
CMC Lead: Haripada Sarker. Ph.D.		
Chief, CMC Branch II: Ali Al Hakim, Ph.D.		

Summary of Critical Issues and Complexities
--

See the following individual IQAs

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

**Following are the Drug Substance (DS) and Drug Product (DP) information as per IQP
5106 (Attachment-1)**

**Initial Quality Assessment
Branch II
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
NDA 207-103**

Background Summary

The application, Pfizer introduces the drug product, Palbociclib, a highly selective, reversible, inhibitor of cyclin-dependent kinases (CDK) 4 and 6, for the treatment of Advanced Breast Cancer (ABC). Palbociclib is a small new molecular entity, formulated as 75 mg, 100 mg, and 125 mg capsules.

The CMC information of the NDA is submitted as per eCTDQ format. Following are the DS and DP information and assessment as per IQP 5106 (Attachment-1)

Drug Substance and Drug Product

1. Document the drug type (e.g., API, dosage form, delivery system).

Palbociclib is a small new molecular entity, formulated as 75 mg, 100 mg, and 125 mg capsules, administered orally.

2. Identify the chemical classification code (as required for PDUFA V).

Palbociclib DS Chemical Class: Class 1

The chemical structure of Palbociclib is confirmed on batch E010013487 (GR06533) by using a combination of elemental analysis, mass spectrometry (MS), nuclear magnetic resonance (NMR) spectroscopy, infra-red (IR) spectroscopy and (b) (4) (b) (4). Supporting evidence is provided by the synthetic route and using known starting materials of defined regiospecificity.

3. If an innovative technology is proposed in the submission, document it and discuss the consequences for the review process.

3.1 DS is identified, synthesized and controlled in a conventional process. The manufacturing process is a conventional, stepwise synthesis using standard procedures. In the final step, Palbociclib is (b) (4).

Manufacturing process also includes the Control of Materials, Control of Critical Steps and Intermediates, in-process-controls and Manufacturing Process Development. A summary of the control strategy is introduced, which provides an overview of the process parameters and analytical controls that indicated to ensure all CQAs for Palbociclib along with Critical process parameters (CPP) of above relevant processing steps.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

3.2 DP is formulated, manufactured and controlled in a conventional process.

Palbociclib is formulated as an immediate release capsule for oral administration at 75 mg, 100 mg, and 125 mg dose strengths. Following Table 4 represents the DP components and composition for one of the strength, 75 mg. Similarly, components and composition of 100 mg and 125 mg capsules are provided.

The DP manufacturing process is described with flow diagram along with process controls. Critical process parameters for the manufacture of Palbociclib capsules have been identified based on the knowledge gained during drug development. The critical processes parameters are part of the overall control strategy, to ensure the critical quality attributes (CQAs). The overall product quality control strategy are tabulated, and includes a combination of input material specifications, established process parameter ranges, in-process controls and finished product specification and testing.

4. Identify what consults will be needed to conduct the review.

For consult, See Item 8 under IQA and Filing Review Cover Sheet

5. Identify required facility input for the EES.

Facilities for DS and DP are entered in EES by PM and verified CMC Lead for Inspection by OC.

6. Summarize key issues from the IND phase.

6a. Specifics of the communications between FDA and the Sponsor.

6b. Whether Sponsor commitments during the IND phase were followed.

Reference is made to list of meeting with FDA, of which CMC related issues are indicated as following. Meeting dated 08 January 2014 - FDA provided written feedback on the CMC development, including the proposed particle size and impurity specifications submitted. Follow up information was submitted on 8 May 2014. 11 February 2014 - Official meeting minutes for a Type B CMC meeting held on 23 January 2014 (Briefing Package submitted on 18 December 2013 [SN0263]). Agreement was reached for the use of unprinted capsules for validation and additional data to be submitted in the NDA. 31 March 2014 - Official meeting minutes for a Type B pre-NDA meeting held on 28 February 2014. During this meeting, the FDA requested additional information on the bioequivalence and formulation of Palbociclib was submitted and discussed.

7. Determine whether there is information (e.g., in the pharmaceutical development, batch analysis and stability sections) for the CMC and Biopharmaceutics reviewers to establish a bridge between the clinical batches and the commercial manufacturing process. The Biopharmaceutics reviewer will determine whether there is information (e.g., dissolution method development report) in an NDA submission.

See biopharm IQA for this issue.

8. Determine whether stability data are sufficient to support an expiration date.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

Drug Substance:

A primary, long-term stability study is ongoing on three batches of Palbociclib (E010014100, E010014101, E010014102) manufactured via the proposed commercial synthetic route and at a scale representative of commercial production. The study is being evaluated over 9 months and DS supportive stability data up to 18 months for two batches. All batches are being tested in accordance with ICH Q1A(R2). Additionally, stability studies have been set down at stressed conditions (thermal, forced degradation and photolytic stress). A summary of the registration stability batches, supportive stability batches and the registration stability protocol are provided in following Table below

Table. Drug Substance Stability Batch Information

Drug Substance Primary Stability Batch Information				
Batch Number	Manufacture Date	Manufacture Site	Batch Size (kg)	Months of Data Available
E010014100	(b) (4)		(b) (4)	9
E010014101				9
E010014102				9
Drug Substance Supportive Stability Batch Information				
Batch Number	Manufacture Date	Manufacture Site	Batch Size (kg)	Months of Data Available
GR06107	(b) (4)		(b) (4)	18
GR06533				12

Stability information for Palbociclib drug substance under long term and accelerated conditions is provided below.

- Data up to 9 months at 25°C/60%RH and 6 months at 40°C/75%RH is provided for three primary batches of Palbociclib drug substance produced using the proposed commercial process. In addition, one primary batch was set up on photostability as per ICH guidance.
- Supportive stability information is also provided for two stability lots (GR06533 & GR06107) up to 12 and 18 months at 25°C/60%RH respectively and 6 months at 40°C/75%RH.
- A stressed stability study was conducted where Palbociclib drug substance was exposed to 70°C/75%RH for 21 days and 70°C/5%RH for 53 days.

The storage conditions used and sampling time-points are presented in Table below

Table. Protocol for storage conditions for the primary stability batches

Storage Condition	Interval (months)*								
	Initial	1	3	6	9	12	18	24	36
25°C/60% RH	A	A	A	A	A	A	B	A	A
40°C/75% RH	-	A	A	A	-	-	-	-	-

* May extend study interval out to 60 months

Based on the available DS stability data, a retest period of (b) (4) months at (b) (4) has been proposed when packaged and sealed in (b) (4).

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

Drug Product

In Wave 1 of rolling submission, Applicant provided 9 months stability data for 9 batches from the primary registration stability program and the 12 months stability data for 3 batches from the supportive stability program. DP stability test data are provided on Palbociclib capsules under long-term, accelerated and thermal/light stressed conditions as per following testing protocol (Table below).

Table: Protocol for Primary Studies of Palbociclib Capsules.

Storage Condition	Interval (months)								
	Initial	3	4.5	6	9	12	18	24	36
Initial/Release	A								
40 °C/75% RH		B	B	B					
30 °C/75% RH		B	B	B	B	A	B	A	A
25 °C/60% RH		B	B	B	B	A	B	A	A
5 °C		C	C	C	C	C	C	C	C

In Wave 2, Applicant provided 12 months DP stability data. 12-months DP stability data appears acceptable pending acceptable CMC review recommendation.

9. List the important DMFs (e.g. drug substance, novel excipients) that are referenced.
For DMF, See section H. MASTER FILES (DMF/MAF) under Review Filing Checklist

9a. Are there letters of authorization?

Yes. See #9 above

9b. Has a deficiency in the DMF been previously identified (e.g., by OGD) and if so has an amendment been submitted?

Not noted. Primary Reviewer may verify and address if any.

9c. Have amendments been submitted since the last review?

Not noted. Primary Reviewer may verify and address if any.

10. Determine whether the application includes Quality by Design elements.

Pfizer is not proposing a design space in this submission. Instead, proven acceptable ranges have been identified for operating parameters. Attributes and parameters have been categorized as either critical or non-critical, based on their impact to the product quality. Where a quality attribute has been designated as critical (critical quality attribute or CQA), associated elements of the control strategy will be explained in detail.

The NDA is not formally submitted as QbD application; however, some elements of QbD are applied in DS and DP manufacturing and quality controls. Primary Reviewer might verify the QbD elements as appropriate.

11. Determine whether the Applicant is proposing a comparability protocol.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

CMC: Pfizer is submitting a comparability protocol to qualify a [REDACTED] (b) (4)

[REDACTED]. This protocol is described in Section 3.2.R Comparability Protocol – Drug Substance. Pfizer is also submitting a comparability protocol to qualify an alternative drug product [REDACTED] (b) (4) of palbociclib capsules 75, 100 and 125 mg capsules at the Pfizer Freiburg, Germany site. This protocol is described in Section 3.2.R Comparability Protocol – [REDACTED] (b) (4)

Additionally, see Biopharm IQA for this issue.

12. Describe issues with drug name, if any.

On 27 November 2013, the Sponsor submitted a request to FDA for review of the proposed proprietary name 'IBRANCE' (IND 69,324, SN 0256). On 08 May 2014, the Sponsor received a letter from the Office of Surveillance and Epidemiology indicating conditional acceptance of the proposed proprietary name.

13. Describe changes between the clinical DP and the proposed commercial DP, if any.

Not noted. Primary Reviewer may verify and address if any.

14. Provide drug substance overview and issues, if any.

Drug Substance Critical Issues

- Verify the designation of regulatory starting material for Olaparib DS.
- Verify CMC issues in CMC related issues in pre-NDA meeting stage.
- Verify the control strategy of the process parameters and analytical controls that ensures CQAs.
- Verify the DS acceptance criteria included in specification.
- Omission of test for solvents from DS specifications.
- Verify the 9 months DS stability test data to justify the retest period of [REDACTED] (b) (4) months.
- EER information for drug substance needs to be re-examined for accuracy.

15. Provide drug substance specification.

The DS controls includes detailed explanation of the origin, fate, purge and control of these impurities, including genotoxic impurities, The control of Palbociclib DS is included in the following Table below.

Table: Specification for Palbociclib Drug Substance.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

TEST	TEST METHOD	ACCEPTANCE CRITERIA
PHYSICAL CHARACTERISTICS		
Appearance	Visual	Yellow to Orange powder
Particle Size	TM-1771A	(b) (4): NMT (b) (4) μ m (b) (4): NMT (b) (4) μ m
IDENTIFICATION		
Infrared Spectroscopy	USP <197>	Infrared absorption spectrum compares to that of the standard of Palbociclib
Liquid Chromatography	TM-1855A	Sample chromatogram exhibits a major peak with the same retention time as that of the standard of Palbociclib
ASSAY		
Liquid Chromatography	TM-1855A	(b) (4) % on an (b) (4)
(b) (4)	USP (b) (4)	NMT (b) (4) %
RESIDUAL SOLVENTS		
(b) (4)	TM-1759A	NMT (b) (4) %
	TM-1759A	NMT %
	TM-1761A	NMT %
INORGANIC IMPURITIES		
Residue on Ignition	USP <281>	NMT (b) (4) %
(b) (4)	TM-1823A	NMT (b) (4) ppm
Heavy Metals	USP <231>	NMT (b) (4) ppm
ORGANIC IMPURITIES		
(b) (4)	TM-1855A	NMT (b) (4) %
	TM-1855A	NMT %
	TM-1855A	NMT (b) (4) %
	TM-1855A	NMT %
Individual unspecified impurities	TM-1855A	NMT %
Total Organic Impurities	TM-1855A	NMT (b) (4) %

Test methods are described along with justification of acceptance criteria. Summary tables detailing the batches of Olaparib used in the toxicological studies, clinical studies and stability studies performed during the development of Palbociclib are presented. The Palbociclib (b) (4) Lot GR06533 was selected for reference standard. DS test data contain batch analyses for lots of PD-0332991-0002 (toxicology studies), PD-0332991-0054 (clinical and toxicology studies), and PD-0332991-00 (clinical and toxicology studies). In addition, test data are provided for DS registration stability batches.

16. Provide Drug Product overview and issues (including as appropriate, containers closure issues like leachables), if any.

The registration stability studies for Palbociclib capsules will justify the acceptability of the proposed commercial container/closure systems listed in Table below.

Table. Packaging Systems, Commercial Product Launch

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

HDPE Bottle/Closure System				
Strength (mg)	Count	Bottle Size (cc)	Closure (mm)	Average MVTR/Unit Ratio (mg/day/capsule)
75	21	60	28	(b) (4)
100	21	60	28	
125	21	60	28	

Drug Product Critical Issues

- Verify CMC issues in pre-NDA meeting (under IND 69324).
- Verify the control strategy of the process parameters and analytical controls that ensures CQAs.
- Verify the Comparability Protocols as described in Item #7 under IQA and Filing Review Cover Sheet.
- Verify the DP acceptance criteria included in specification
- Prepare Method Validation consult for DS as the new molecular entity.
- DMFs for container/closure systems need to be reviewed for adequacy of the NDA.
- Justification of (b) (4) months expiration based on available stability data
- The DP labeling need to be evaluated for its relevant CMC sections.
- Check EES of DP sites for accuracy.

17. Provide composition of drug product.

Palbociclib is formulated as an immediate release capsule for oral administration at 75 mg, 100 mg, and 125 mg dose strengths. Following Table represents the DP components and composition for one of the strength, 75 mg. Similarly, components and composition of 100 mg and 125 mg capsules are provided.

Table. Composition of Olaparib 75 mg capsules

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

Name of Ingredients	Reference to Standard	Function	Unit Formula	
			Unit (mg)	%
Blend Composition				
Palbociclib	Pfizer	Drug Substance	75.000 ¹	(b) (4)
Microcrystalline Cellulose (b) (4)	USP/NF, Ph Eur., JP			(b) (4)
Lactose Monohydrate	USP/NF, Ph Eur., JP			
Sodium Starch Glycolate (Type A)	USP/NF, Ph Eur., JP			
Colloidal Silicon Dioxide	USP/NF, Ph Eur., JP			
Magnesium Stearate	USP/NF, Ph Eur., JP			
Total Target Fill Weight				
Hard Gelatin Capsule Shell				
Capsule Shells (Size #2, (b) (4) HG Capsules) ^{3,4}	Pfizer	Encapsulation	1 capsule	
Body (b) (4)				(b) (4)
Gelatin	USP/NF, Ph Eur., JP			(b) (4)
Red Iron Oxide (b) (4)	USP/NF, JP			
Yellow Iron Oxide (b) (4)	USP/NF, JP			
Titanium Dioxide (b) (4)	USP/NF, Ph Eur., JP			
Cap (b) (4)				
Gelatin	USP/NF, Ph Eur., JP			
Red Iron Oxide (b) (4)	USP/NF, JP			
Yellow Iron Oxide (b) (4)	USP/NF, JP			
Titanium Dioxide (b) (4)	USP/NF, Ph Eur., JP			
Approximate Weight of Capsule Shell				
Print Ink ⁴				
Approximate Weight of Ink on Capsule Shell				(b) (4)

N/A is not applicable; HG is hard gelatin; qsp is sufficient quantity

- 1 (b) (4)
- 2 (b) (4)
- 3 (b) (4)
- 4 The body is pre-printed with "PBC 75" and the cap pre-printed with "Pfizer" with (b) (4) White. Printing ink contains Shellac (b) (4) in (b) (4) (USP/NF, Ph Eur., JP), Titanium Dioxide (USP, FCC, Ph Eur., JP) (b) (4) (USP, Ph Eur., JP), Ammonium Hydroxide (b) (4) Propylene Glycol (USP, FCC, Ph Eur., JP, JSFA) (b) (4) and Simethicone USP/Simethicone Ph Eur. (b) (4)
- 5 (b) (4)

The three commercial capsule strengths are prepared (b) (4) utilizing conventional pharmaceutical excipients (b) (4). The dosage strengths are differentiated by capsule shell size, color, and printing, using globally acceptable components.

The batch formula for palbociclib capsules 75 mg, 100 mg, and 125 mg are presented in Table 5. A (b) (4) to manufacture all capsule strengths. The weight of the (b) (4) has a range from (b) (4) kg to (b) (4) kg. The typical drug product batch sizes manufactured at Pfizer Manufacturing Deutschland GmbH correspond to the proposed validation batch sizes between (b) (4) kg for the 75 mg capsules, (b) (4) kg for the 100 mg capsules and (b) (4) kg for the 125 mg capsules. (b) (4) based on the (b) (4) formulation.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (*CMC and Biopharmaceutics*)**

The DP manufacturing process is described with flow diagram along with process controls. Critical process parameters for the manufacture of Palbociclib capsules have been identified based on the knowledge gained during drug development. The critical processes parameters are part of the overall control strategy, to ensure the critical quality attributes (CQAs). The overall product quality control strategy are tabulated, and includes a combination of input material specifications, established process parameter ranges, in-process controls and finished product specification and testing.

18. Provide drug product specification.

The DP specification is presented in following Table.

Table. Release Specification of Palbociclib 75 mg, 100, and 125 mg Capsules.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

Test	Test Method	Acceptance Criteria
Physical Characteristics		
Appearance	Visual	<p>75 mg: Size #2, opaque, hard capsule, with a light orange body color (printed "PBC 75" in white) and a light orange cap color (printed "Pfizer" in white). The capsule contains an (b) (4) powder.</p> <p>100 mg: Size #1, opaque, hard capsule, with a light orange body color (printed "PBC 100" in white) and a caramel cap color (printed "Pfizer" in white). The capsule contains an (b) (4) powder</p> <p>125 mg: Size #0, opaque, hard capsule, with a caramel body color (printed "PBC 125" in white) and a caramel cap color (printed "Pfizer" in white). The capsule contains an (b) (4) powder.</p>
Identification¹		
LC-retention time	TM-1876A	Retention time of main band in the sample corresponds to that of the standard
LC-UV spectra	TM-1876A	UV spectrum of main band in sample corresponds to that of the standard
Assay		
Assay (LC)	TM-1876A	(b) (4) % of label claim
Degradation Products (LC)		
Unspecified Degradation Products	TM-1876A	NMT (b) (4) % (each)
(b) (4)	TM-1876A	NMT (b) (4) %
Total Degradation Products	TM-1876A	NMT (b) (4) %
Dissolution		
Dissolution	TM-1877A	Conforms to USP <711> requirements where not less than (b) (4) % (Q) of the label claim is dissolved in 30 minutes
Uniformity of Dosage Units¹		
Weight Variation	USP <905>	Conforms to USP <905> requirements
(b) (4)	(b) (4)	NMT (b) (4) %
Microbial Limits²		
Total Aerobic Microbial Count	USP <61>	NMT (b) (4) cfu/g
Total Yeasts and Molds	USP <61>	NMT (b) (4) cfu/g
<i>Escherichia coli</i> ¹	USP <62>	Absence in 1 g
(b) (4)		

Test methods, and justification of acceptance criteria for each attributes are presented.

Applicant provided summaries of data for all batches of 5 mg, 25 mg and 100 mg Phase 1/2 isethionate capsules, as well as all batches of 75 mg, 100 mg and 125 mg phase 3 freebase capsules.

Analytical data are presented on DP batches of Palbociclib capsules manufactured at the commercial scale during development. All DP batches were manufactured at the commercial site, Pfizer, Germany. All of the batches indicated to comply with the proposed commercial specification. The primary degradation product observed in Palbociclib capsules is (b) (4),

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

(b) (4). This structure has been analyzed, and found to contain no structural alerts. All other degradation products are indicated during release testing or on stability have remained at levels below the qualification threshold as stated in the ICH Guideline Q3B(R2).

Microbial method and acceptance criteria have been established for palbociclib capsules, and are appropriate for the intended use. The proposed acceptance criteria assure that the finished product will meet the acceptance criteria aligned with harmonized acceptance criteria for microbiological quality of (b) (4) preparations for oral use (USP <1111>).

Addition Item: Overall CMC Recommendation:

Comments and Recommendations from Quality (CMC)

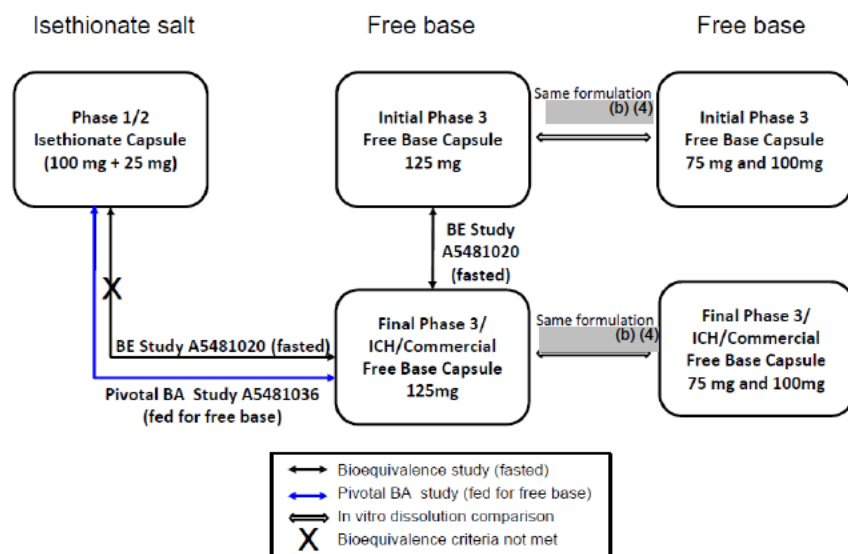
The application is fileable; no 74-Day Letter issues regarding drug product stability have been identified at this point. Facilities have been entered into EES for inspection. The manufacturing process is not particularly complex. If priority, two CMC reviewers are recommended for this NDA.

Biopharmaceutics Assessment

Biopharmaceuticals Critical Issues or Complexities

Biopharmaceutics Summary

Palbociclib has been formulated as an immediate release oral capsule for use in combination with letrozole, for the treatment of postmenopausal women with estrogen receptor (ER)-positive, human epidermal growth factor receptor 2 (HER2)-negative advanced breast cancer who have not received previous systemic treatment for their advanced disease. The sponsor seeks NDA approval through the accelerated approval pathway relying on clinical efficacy from a single open-label, randomized, Phase 1/2 study (A5481003). A Phase 3 confirmatory study will be completed post approval. The Phase 1/2 study used an early, (b) (4) capsule formulation of the isethionate salt drug substance. However, for the confirmatory Phase 3 and commercial product, an automated, large scale production process was developed using the free base drug substance. The formulation bridging scheme is illustrated below.



Bioequivalence was not demonstrated between the pivotal clinical trial material and the proposed commercial product; however the Applicant has submitted additional relative bioavailability studies and exposure-response analysis to support approval of the proposed commercial product. These data will be reviewed by the Office of Clinical Pharmacology. Biopharmaceutics will focus of the relative BA studies used to set manufacturing specifications and the acceptability of the proposed dissolution method and acceptance criteria.

Critical Review Issues/Complexities

None.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

FILING REVIEW CHECKLIST

The following parameters are necessary in order to initiate a full review, i.e., complete enough to review but may have deficiencies. On **initial** overview of the NDA application for filing:

A. GENERAL				
	Parameter	Yes	No	Comment
1.	Is the CMC section organized adequately?	Yes		
2.	Is the CMC section indexed and paginated (including all PDF files) adequately?	Yes		
3.	Are all the pages in the CMC section legible?	Yes		
4.	Has all information requested during the IND phase, and at the pre-NDA meetings been included?	Yes		

B. FACILITIES*				
* If any information regarding the facilities is omitted, this should be addressed ASAP with the applicant and can be a <i>potential</i> filing issue or a <i>potential</i> review issue.				
	Parameter	Yes	No	Comment
5.	Is a single, comprehensive list of all involved facilities available in one location in the application?	Yes		See the List of Facilities in CMC IQA.
6.	For a naturally-derived API only, are the facilities responsible for critical intermediate or crude API manufacturing, or performing upstream steps, specified in the application? If not, has a justification been provided for this omission? This question is not applicable for synthesized API.			Not applicable.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

	Parameter	Yes	No	Comment
7.	<p>Are drug substance manufacturing sites identified on FDA Form 356h or associated continuation sheet? For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Yes		
8.	<p>Are drug product manufacturing sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list:</p> <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Yes		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

	Parameter	Yes	No	Comment
9.	Are additional manufacturing, packaging and control/testing laboratory sites identified on FDA Form 356h or associated continuation sheet. For each site, does the application list: <ul style="list-style-type: none"> • Name of facility, • Full address of facility including street, city, state, country • FEI number for facility (if previously registered with FDA) • Full name and title, telephone, fax number and email for on-site contact person. • Is the manufacturing responsibility and function identified for each facility?, and • DMF number (if applicable) 	Yes		
10.	Is a statement provided that all facilities are ready for GMP inspection at the time of submission?	Yes		

C. ENVIRONMENTAL ASSESMENT

	Parameter	Yes	No	Comment
11.	Has an environmental assessment or claim of categorical exclusion been provided?	Yes		Claim of categorical exclusion has been provided.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

D. DRUG SUBSTANCE/ACTIVE PHARMACEUTICAL INGREDIENT (DS/API)				
	Parameter	Yes	No	Comment
12.	Does the section contain a description of the DS manufacturing process?	Yes		
13.	Does the section contain identification and controls of critical steps and intermediates of the DS?	Yes		
14.	Does the section contain information regarding the characterization of the DS?	Yes		
15.	Does the section contain controls for the DS?	Yes		
16.	Has stability data and analysis been provided for the drug substance?	Yes		
17.	Does the application contain Quality by Design (QbD) information regarding the DS?		No	Some QbD elements are utilized to justify the attributes.
18.	Does the application contain Process Analytical Technology (PAT) information regarding the DS?		No	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

E. DRUG PRODUCT (DP)				
	Parameter	Yes	No	Comment
19.	Is there a description of manufacturing process and methods for DP production through finishing, including formulation, filling, labeling and packaging?	Yes		
20.	Does the section contain identification and controls of critical steps and intermediates of the DP, including analytical procedures and method validation reports for assay and related substances if applicable?	Yes		
21.	Is there a batch production record and a proposed master batch record?	Yes		
22.	Has an investigational formulations section been provided? Is there adequate linkage between the investigational product and the proposed marketed product?	Yes		
23.	Have any biowaivers been requested?	Yes		
24.	Does the section contain description of to-be-marketed container/closure system and presentations?	Yes		
25.	Does the section contain controls of the final drug product?	Yes		
26.	Has stability data and analysis been provided to support the requested expiration date?	Yes		Stability data and analysis been provided to support the commercially viable shelf-life.
27.	Does the application contain Quality by Design (QbD) information regarding the DP?		No	Some QbD elements are utilized to justify the attributes.
28.	Does the application contain Process Analytical Technology (PAT) information regarding the DP?		No	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

F. METHODS VALIDATION (MV)				
	Parameter	Yes	No	Comment
29.	Is there a methods validation package?	Yes		Consult request has been made to Division of Pharmaceutical Analysis Attn: Michael Trehy, PhD Suite 1002 1114 Market Street St. Louis, MO 63101

G. MICROBIOLOGY				
	Parameter	Yes	No	Comment
30.	If appropriate, is a separate microbiological section included assuring sterility of the drug product	Yes		

H. MASTER FILES (DMF/MAF)				
	Parameter	Yes	No	Comment
31.	Is information for critical DMF references (i.e., for drug substance and important packaging components for non-solid-oral drug products) complete?	Yes		LoA provided. See below for detail.

Table. DMF Information.

DMF #	TYPE	HOLDER	ITEM REFERENCED	LOA DATE	COMMENTS
(b) (4)	III		(b) (4)	Yes	Not applicable
	III			Yes	Not applicable
	IV			Yes	Not applicable
	IV			Yes	Not applicable
	III			YES	Not applicable
	III			Yes	Not applicable
	III			Yes	Not applicable
	III			Yes	Not applicable

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

I. LABELING				
	Parameter	Yes	No	Comment
32.	Has the draft package insert been provided?	Yes		
33.	Have the immediate container and carton labels been provided?	Yes		

J. BIOPHARMACEUTICS																				
Initial - Overview of the NDA application for filing																				
	Parameter	Yes	No	Comment																
34.	Does the application contain dissolution data?	X																		
35.	Is the dissolution test part of the DP specifications?	X		<table><tr><th colspan="2">Dissolution Method</th></tr><tr><td>Apparatus</td><td>USP 2</td></tr><tr><td>Medium</td><td>0.1 N HCl</td></tr><tr><td>Agitation speed</td><td>50 rpm</td></tr><tr><td>Temperature</td><td>37 °C</td></tr><tr><td>Sampling Times</td><td>30 minutes</td></tr><tr><td>Analytical Method</td><td>UV detection</td></tr><tr><td>Acceptance Criterion</td><td>Q = ^(b)₍₄₎ % in 30 min</td></tr></table>	Dissolution Method		Apparatus	USP 2	Medium	0.1 N HCl	Agitation speed	50 rpm	Temperature	37 °C	Sampling Times	30 minutes	Analytical Method	UV detection	Acceptance Criterion	Q = ^(b) ₍₄₎ % in 30 min
Dissolution Method																				
Apparatus	USP 2																			
Medium	0.1 N HCl																			
Agitation speed	50 rpm																			
Temperature	37 °C																			
Sampling Times	30 minutes																			
Analytical Method	UV detection																			
Acceptance Criterion	Q = ^(b) ₍₄₎ % in 30 min																			
36.	Does the application contain the dissolution method development report?	X		Section 3.2.P.2.2, part of the drug product development report.																
37.	Is there a validation package for the analytical method and dissolution methodology?	X		Summary information provided in Section 3.2.P.5.3, full report not included.																
38.	Does the application include a biowaiver request?		X																	
39.	Does the application include an IVIVC model?		X																	
40.	Is information such as BCS classification mentioned, and supportive data provided?	X		BCS Class ^(b) ₍₄₎ reported																
41.	Does the application include information/data on in vitro alcohol dose-dumping potential?		X																	
42.	Is there any in vivo BA or BE information in the submission?	X																		

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceutics)**

43.	Is any of the in vivo BA or BE under Biopharmaceutics review as per the Sept 2013 MOU)?	X	<p>Bioequivalence was not demonstrated between the pivotal clinical and commercial formulation. The relative BA studies to support approval of the proposed formulation change and exposure-response analyses will be reviewed by the Office of Clinical Pharmacology.</p> <p><i>Study 1022</i> (relative BA to evaluate particle size effects) will be reviewed by Biopharm.</p>
44.	Is the to-be marketed formulation the same as used in clinical studies? If no, are bridging data submitted for review?	X	<p>See comment above. The commercial formulation is different from the pivotal Phase 1/2 study, but the in vivo bridging data will be reviewed by the Office of Clinical Pharmacology.</p> <p>The in vitro dissolution data will be reviewed by Biopharmaceutics.</p>

FILING CONCLUSION (Quality)				
	Parameter	Yes	No	Comment
45.	ARE THE PRODUCT QUALITY AND BIOPHARMACEUTICS SECTIONS OF THE APPLICATION FILEABLE?	<input checked="" type="checkbox"/>		
46.	If the NDA is not fileable from the product quality perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
47.	If the NDA is not fileable from the biopharmaceutics perspective, state the reasons and provide filing comments to be sent to the Applicant.			N/A (fileable)
48.	Are there any potential review issues identified?	<input type="checkbox"/>	<input checked="" type="checkbox"/>	

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marketing Applications (CMC and Biopharmaceutics)**

This document will be sequentially signed in DARRTS by all of the following who authored or reviewed this assessment:

See appended electronic signature page

Haripada Sarker, Ph.D.
CMC Lead
(Reviewer, CMC of IQA)
Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment

See appended electronic signature page

Minerva Hughes, Ph.D.
Biopharmaceutics Reviewer
Office of New Drug Quality Assessment

See appended electronic signature page

Okpo Eradiri, Ph.D.
Acting Biopharmaceutics Team Leader (for Angelica Dorantes)
Office of New Drug Quality Assessment

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Ali Al-Hakim, Ph.D.
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Division of Pre-Marketing Assessment I, Branch II
Office of New Drug Quality Assessment

ONDQA Initial Quality Assessment (IQA) and Filing Review For Pre-Marking Applications (CMC and Biopharmaceuticals)

Attachment-1

NDA RISK ASSESSMENT TABLE (Capsules). Table Completed by CMC Lead. Also see Foot Notes.

Product attribute/CQA	Factors that can impact the CQA	Probability* (O)	Severity of Effect* (S)	Detectability* (D)	FMECA RPN Number**	Comment	Risk***
Assay, stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	4	2	Release and Stability (2)	16	12 months stability data provided.	L
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	3 (b) (4)	2	3	18	Highly soluble DS.	L
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	4 (Drug Loading (b) (4) %)	3	3	36		M
Dissolution	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	3	2	2	12	ONDQA BioPharm will assess	L
Microbial limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	1	2	3	6	OPS Micro will assess	L

Notes: * Range 1-5 (1-low, 5-high); **RPN#= O × S × D. *** RPN Values: Low Risk (1-25); Moderate Risk (26-60); High Risk (61-125).
Source of the NDA RISK ASSESSMENT TABLE: From various presentations on OPQ reorganization.

The evaluation from the IQA table was transferred to the following NDA table that can be used by the primary reviewer as a part of the NDA review.

**ONDQA Initial Quality Assessment (IQA) and Filing Review
For Pre-Marking Applications (CMC and Biopharmaceuticals)**

NDA RISK ASSESSMENT TABLE (To be Completed by primary CMC reviewer)

From Initial Quality Assessment			Review Assessment		
Product attribute/ CQA	Factors that can impact the CQA	Risk Ranking	Risk Mitigation approach	Risk Evaluation	Lifecycle Considerations / Comments
Assay, stability	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	L			
Physical stability (solid state)	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L			
Content Uniformity	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	M			
Dissolution	<ul style="list-style-type: none"> • Formulation • Container closure • Raw materials • Process parameters • Scale/equipment • Site 	L			
Microbial limits	<ul style="list-style-type: none"> • Formulation • Raw materials • Process parameters • Scale/equipment • Site 	L			

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

HARIPADA SARKER
09/17/2014

MINERVA HUGHES
09/17/2014

OKPONANABOFA ERADIRI
09/17/2014

ALI H AL HAKIM
09/17/2014